

REVIEW ARTICLE



Kaposi's sarcoma: Insights into its understanding

K. Badari Rao

Associate Professor, Department of Oral Pathology & Microbiology, NSVK Sri Venkateshwara Dental College & Hospital, Bannerughatta, Bengaluru - 560 083, Karnataka, India

Correspondence

K. Badari Rao,
Department of Oral Pathology &
Microbiology, NSVK Sri Venkateshwara
Dental College & Hospital, Bannerughatta,
Bengaluru - 560 083, Karnataka, India.
Phone: +91-9902028816,
E-mail: dr.badarirao@gmail.com

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Abstract

Kaposi's sarcoma (KS) is a common vascular tumor arising in human immunodeficiency virus (HIV) infected patients and is one of the 27 conditions designated by the Centers for Disease Control as an acquired immunodeficiency syndrome (AIDS) defining illness. Human herpes virus-8 (HHV-8), now called KS-associated herpes virus (KSHV), is a member of γ herpes virus family and is considered as the causative agent of KS. This review aims to discuss KS and its association with HIV/AIDS with an emphasis on oral features, the role of HHV-8/KSHV in causation of KS, and the current challenges faced in the management of the disease.

Keywords: Acquired immunodeficiency syndrome, human herpes virus-8, Kaposi's sarcoma, Kaposi's sarcoma-associated herpes virus

Introduction

In 1869, Helmut Kobner, a German physician, appears to have been the first to describe cases of metastatic cutaneous sarcoma. In 1872, the Hungarian physician, Moricz Kaposi, described an idiopathic, multi-pigmented, tumor-like lesion of the skin that eventually was named Kaposi's sarcoma (KS).^[1,2] During the 19th century, KS was considered a rare disease and by the early 20th century, an increased incidence was suggested.^[2,3] KS is now a common vascular tumor arising in human immunodeficiency virus (HIV) infected patients, and is one of the 27 conditions designated by the Centers for Disease Control as an acquired immunodeficiency syndrome (AIDS) defining illness.^[2,4] Human herpes virus-8 (HHV-8), also called KS-associated herpes virus (KSHV), a member of γ herpes virus family, is considered to be the causative agent of KS.^[5]

Clinical features

Based on epidemiology and demographics, there are four variants of KS: (1) Classic KS that is relatively benign and predominantly occurs in elderly patients of Mediterranean, European, or Middle Eastern origin with a median age of >70 years; (2) an endemic or "African" form of KS that also occurs predominantly in men at a ratio of 3:1 with a peak median age of 35-39 years; (3) iatrogenic or post-transplant KS that may occur in HIV-seronegative

immunocompromised individuals, long-term users of steroids and cytotoxic drugs, and individuals with autoimmune disorders; and (4) AIDS-associated KS. Although the four variants of KS are distinctive, they share similar clinical and histologic features, suggestive of the common pathogenesis.^[5] In contrast to classic KS, which is often limited to the extremities, AIDS-associated KS frequently involves the mucocutaneous regions of the head and neck as primary sites, and visceral involvement is also present.^[6] Mucocutaneous lesions of the head and neck region, occur in estimated 10% of AIDS patients.^[7] The oral cavity is frequently involved with the hard and soft palate, gingiva, and tongue being the most common sites.^[8,9] The prevalence of oral KS varies from 0 to 12% in Africa, and from 0 to 38% in United States and Europe.^[10,11] Since the advent of AIDS, a high prevalence of oral KS is also noted in HIV-infected patients in Zimbabwe.^[12]

Based on clinical appearance, AIDS-associated KS is classified into six overlapping types: patch, plaque, telangiectatic, nodular, florid, and infiltrative.^[1,3,13,14] Oral lesions appear as red to purple macules, papules, or nodules that may ulcerate and cause local destruction.^[9,15] Although the clinical behavior of AIDS-associated oral KS is rather unpredictable, majority of the cases represent aggressive disease and have associated disseminated cutaneous and visceral lesions.^[16] Slow growing oral tumors are generally associated with patients who have no additional complicating opportunistic infections.^[17]

Differential diagnosis

Early lesions of KS may be difficult to distinguish from ecchymoses, nevi, dermatofibroma and lichen planus.^[18] Nodular or plaque-like lesions overlying mucosa should be biopsied to rule out bacillary angiomatosis, hemangioma, pyogenic granuloma, angiosarcoma, or lymphangiosarcoma.^[18,19]

Histopathology

The histogenesis of KS is difficult to determine as lesions typically exhibit multiple cell types. The tumor is mainly composed of undifferentiated mesenchymal cells and spindle-shaped cells.^[20-23] The spindle cells, considered the tumor element, are of mesenchymal origin and have features that resemble both endothelial and smooth muscle cells.^[22,23] The tumor cells may be derived from cells of either lymphatic or venous differentiation.^[17,22] Furthermore, biopsies of KS feature numerous slit-like vascular channels and may present extravasation of erythrocytes, hemosiderophages, eosinophilic hyaline inclusions, and inflammatory infiltrate.^[9,20,21]

The histogenesis of the spindle cell component, believed to be the KS tumor cell, remains controversial; although many studies favor an endothelial cell origin.^[22-24] Another highly debatable issue is whether KS is a clonal "neoplastic" lesion or whether it is "reactive" and polyclonal. Most of the evidence suggests that many KS lesions are hyperplastic and polyclonal in nature, but that either,

- These lesions contain a small proportion of clonal, neoplastic tumor cells that are difficult to identify and culture, or
- Some of these polyclonal lesions may undergo full transformation during disease progression, probably when an actively proliferating cell acquires genetic alterations that provide a selective advantage, leading to the emergence of a truly neoplastic clone in the minority of cases of KS.^[24]

Role of HHV-8/KSHV and HIV

Multiple agents, including cytomegalovirus, hepatitis-B virus, HHV-6, HIV, and *Mycoplasma penetrans*, have been suspected in the past as causing KS; but none of these have been clearly shown to present in most cases and to have a causal association with KS.^[24] Thus, although an infectious origin has long been suspected, it was only in 1994 that HHV-8/KSHV was first detected in KS specimens.^[25] KSHV is now considered the causative agent of AIDS-associated, classic, endemic, and iatrogenic KS. In addition, it is also believed to be the causative agent of primary effusion lymphomas (body cavity-based lymphomas),^[26] multicentric Castelman's disease,^[26,27] and possibly oral plasmablastic lymphomas.^[28]

Serological studies have indicated that unlike other HHVs, KSHV is not ubiquitous.^[26] The seroprevalence of KSHV is low in the United States and parts of Europe (ranging from 0 to 20%), rising in Mediterranean countries to reach levels >50% in some geographic regions of Africa.^[12] In North America

and Europe, primary infection with KSHV mainly occurs among adult homosexual men and is transmitted principally via sexual contact; the KSHV seroprevalence being associated with the number of sexual partners and sexual practices.^[12,26] Transmission of KSHV via saliva has also been documented.^[29] In African populations, KSHV infection seems to occur largely before puberty through casual family and community contacts; oral secretions being a potential vehicle of non-sexual horizontal spread; vertical transmission of KSHV being insignificant.^[12,26] A recent study conducted in Malawi, Africa, has also shown that, apparently, healthy people in regions where KSHV is endemic can be infected by multiple strains.^[30] However, it is still unclear if this reflects a simultaneous co-infection by several KSHV strains, reactivation of latent strains or superinfection.^[30]

KSHV is lymphotropic and is more closely related to Epstein-Barr virus and herpesvirus saimiri than to other herpes viruses.^[5,27] The KSHV genome contains several genes related to cellular genes involved in cell proliferation and host responses that probably contribute to viral pathogenesis.^[26,31]

The pathogenesis of AIDS-associated KS is multifactorial and involves KSHV, altered expression and response to cytokines and stimulation of KS growth by HIV trans-activation protein (*tat*).^[32,33] KSHV is a necessary but solely not a sufficient cause of KS.^[34] It encodes protein homologs of interleukin-6, chemokines of the macrophage inflammatory protein family, cell cycle regulators of the cyclin family, and anti-apoptotic genes of the bcl-2 family.^[26] The HIV *tat* protein can promote the growth of spindle cells of endothelial origin but only in the presence of inflammatory cytokines.^[32,33] The synergistic relationship between inflammatory cytokines and HIV *tat* protein, when combined with the immunosuppression associated with AIDS, may provide an explanation for aggressive nature of AIDS-associated KS compared to relatively non-aggressive, classic Mediterranean form in which the HIV *tat* protein does not play a role.^[33] The sequence of events creating the inflammatory angiogenic environment has been described by Dezube^[33] as follows: (1) circulating KS progenitor cells and cells latently infected with KSHV seek sites of pre-existing inflammation; in the case of oral KS, pre-existing inflammation may include acute and/or chronic periodontal disease sites; (2) exposure to inflammatory cytokines such as interferon- α (IFN- α) results in differentiation of latently infected cells into KS-like spindle cells and induces KSHV reactivation; (3) reactivation of KSHV leads to expression of potentially pathogenic genes such as viral interleukin-6 that in turn, can activate vascular endothelial growth factor and induce angiogenesis; (4) viral lytic replication in the same cells activates inflammation, which also may play a role in angiogenesis; (5) the creation of inflammatory-angiogenic environment increases the availability of infectable cells, i.e. endothelial and KS spindle cells, which are then included in the development of the lesion; (6) cells also become responsive to HIV *tat* protein; and (7) the HIV *tat* protein augments the inflammatory-angiogenic state by the increasing angiogenic activities of basic fibroblast growth factor, IFN- α , and vascular endothelial growth factor by mimicking the effects of

the external matrix proteins fibronectin and vitronectin and by increasing the expression of matrix metalloproteinases.

Prognosis and management

The prognosis of patients with AIDS-associated KS is often actually dependent on factors other than the tumor itself. In 1989, the AIDS trial council group devised the TIS staging system, based upon the extent of tumor (T), the status of immune system i.e. CD⁴⁺ T-cell count (I), and the presence of other HIV/AIDS-associated systemic diseases (S).^[12]

At present, there is no specific treatment for AIDS-associated KS. Treatment is thus directed towards the elimination, or at least reduction of cosmetically unacceptable lesions, pain, and edema, as well as providing relief from symptoms caused by systemic involvement.^[33] Local therapy may be effective for a limited form of the disease, but systemic therapy is required for disseminated, severe forms of KS.^[33] Highly active anti-retroviral therapy (HAART) is useful in the management of AIDS-associated KS. It can effectively reduce the viral load (HIV) and thereby raise the CD⁴⁺ T-cell count, the two factors which contribute to the causation of KS. Thus, HAART causes fall in KSHV levels in the blood presumably due to a reduction in HIV-induced immunosuppression and HIV/KSHV-mediated oncogenesis.^[12] Reports also suggest a reduced incidence of KS in HIV-infected individuals treated with HAART that includes at least one protease inhibitor. Both *in vivo* and *in vitro* studies have proved the fact that protease inhibitors have a direct anti-angiogenic, anti-tumor activity.^[12]

Older treatment modalities for managing oral KS have been surgical/laser therapy, local irradiation, intra-lesional injections of sodium tetradecyl sulfate, and chemotherapy with vinca alkaloids, paclitaxel and liposomal anthracyclines. However, only five agents are commonly used with success for the treatment of KS: Alitretinoin gel for topical therapy, liposomal daunorubicin and oloxorubicin, paclitaxel, and IFN- α for systemic therapy.^[12]

The strong angiogenic component of KS makes it particularly suitable for treatment with drugs that have anti-angiogenic action, such as thalidomide, matrix metalloproteinases, and IM-862. Based on the apoptotic and anti-proliferative activity of iron chelation on KS cells, it is also suggested that withdrawal strategies may be effective.^[12]

Direct antiviral approaches targeting KSHV have also been proposed. *In vitro* studies have shown that KSHV is very sensitive to cidofovir, moderately sensitive to ganciclovir, but only weakly sensitive to acyclovir. However, their efficacy *in vivo* is yet to be corroborated. IFN- α may inhibit infection or reactivation by KSHV. Single-agent therapy with IFN- α is associated with significant toxicity, but when used in combination with anti-retroviral agents, may have significant effects on disseminated, but non-rapidly progressive KS.^[12]

Conclusions

Studies pertaining to KS suggest epidemiologic patterns that are consistent with a sexually transmitted agent, before a viral

agent HHV-8/KSHV was identified, and that it is strictly not an opportunistic infectious agent related to HIV/AIDS-associated KS. Immune suppression along with genetic and/or environmental factors may interplay in variable combinations in the eventual causation of KS.

Currently, a wide array of treatment modalities for KS, are aimed at elimination of cosmetically unacceptable lesions, reduction of unsightly edema and lymphadenopathy, and to alleviate symptoms caused by systemic involvement.

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